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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,948	10/17/2005	Dennis E. Hallahan	1242/57 PCT/US	9401
25297 7590 03/18/2009 JENKINS, WILSON, TAYLOR & HUNT, P. A. Suite 1200 UNIVERSITY TOWER 3100 TOWER BLVD., DURHAM, NC 27707			EXAMINER GEMBEH, SHIRLEY V	
			ART UNIT 1618	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/523,948	<b>Applicant(s)</b> HALLAHAN ET AL.	
	<b>Examiner</b> SHIRLEY V. GEMBEH	<b>Art Unit</b> 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 08 December 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-4 and 6-46 is/are pending in the application.
- 4a) Of the above claim(s) 14 and 18-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-13 and 15-17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-4 and 6-46 are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                      |                                                                   |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____                                                          | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. The response filed on 12/8/08 has been entered.
2. Applicant's arguments filed 12/8/08 has been fully considered but they are not deemed to be persuasive.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
4. Claims 1-4, 6-14 and 15-46 are pending in this office action. Claims 14 and 18-46 are withdrawn based on the restriction requirement. Claim 5 is cancelled. Claims 1-4, 6-13 and 15-17 are rejected in this office action.
5. The objection of claim 1 is withdrawn due to the amendment of claim 1 to specifically spell out the abbreviated.
6. Claims 1-4 and 6-9 stand rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for using LY294002, Wortmannin, SU6668, SU11248 and Genistein, does not reasonably provide enablement for the administration of undefined P13k antagonists to an unknown target tissue in a subject, for the reasons made of record in Paper No. 20080606 and as follows.

Applicant argues that the instant application as filed recites that a P13K antagonist is a molecule or other chemical entity having a capacity for specifically binding to P13K to inhibit a P13K activity (page 12, lines 27-29). Applicant also argues that the instant application provides working example showing that several small molecule P13K antagonist of varying structure enhance the radiosensitivity of tumors.

In response The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Claims 1-4 and 6-9 encompass using a very wide variation of P13K antagonists on a wide variation of endothelial tissues and vasculature supplying blood flow. Claims 10-13 recite use of Wortmannin and LY294002 which Bridgette et al (J. Clin. Oncol. 21(14), 2003: 2760-2776) teach are inhibitors of PI3K. At present, few studies have reported the in vivo antitumor activity of wortmannin and LY294002. For example **in human pancreatic cancer** xenografts, wortmannin administered daily at twice the maximum-tolerated dose for 10 days **has been shown to cause 100% host mortality**, indicating **its narrow therapeutic index**. Target specificity is also a concern, because these agents can also inhibit other PI3K proteins in normal tissues. The recitation of administering P13K antagonists generically encompasses a wide variation of compounds which might or might not be capable of increasing radiosensitivity of a radiation resistant tumor..... or a target tissue. Structure activity relationship should be considered because not every P13K antagonist would reasonably show potency to increasing radiosensitivity of radiation resistant tumors... or a large variety of target tissues.

Thus the current claims are not commensurate in scope with the limited guidance provided in the specification, and therefore, would require undue experimentation for the skilled artisan to reasonably discover how to make the currently claimed invention work, especially when the prior art recognizes a narrow therapeutic index using the same compounds as in Applicant's disclosure.

7. Claim 8 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reason made of record in Paper No. 20080606 and as follows.

Applicant's argument is found not persuasive. The term " minimally therapeutic dose " in claim 8 is a relative term which renders the claim indefinite. The term " minimally therapeutic dose " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Therefore, what is meant by "administering a minimally therapeutic dose" means remains unknown.

8. Claims 1-4, 6-13 and 15-17 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Although instant claim 1 has been amended to remove the recitation ... "target tissue ..." in the preamble, the method step (a) still recites "...target tissue..." which

makes it confusing as to whether the "...radiation resistant tumor" is the target tissue or the "target tissue" may be any other tissue.

9. Claims 1-4, 6-10 and 12-13 stand rejected under 35 U.S.C. 102(e) as being anticipated by Durden (US 6,777,439), for the reasons made of record in Paper No. 20080606 and as follows.

Consistent with the 112-second paragraph rejection (see paragraph 7) above, the claims are confusing because method step (a) still recites "target tissue" (thus not limited to radiation resistant tumor) but that any tissue may be a "target tissue".

In summary, Durden teach regulating p53 mediated gene expression by administering P13kinase inhibitors to increase chemosensitivity/radiosensitivity of tumor cells (brain tumors) which contains epithelium and vasculature, wherein the PI3k antagonist is LY294002. See col. 2, lines 29-31, 45-55 and 64-67, col. 3, lines 1-3 and col. 7, lines 9-40 as required by instant claims 1, 4, 8 and 12.

10. Claims 1-4, 6-9 and 15 stand rejected under 35 U.S.C. 102(a) as being anticipated by National Cancer Institute (NCI 2001), for the reasons made of record in paper no. 20080606 and as follows.

Consistent with the 112-second paragraph rejection above (see paragraph 7) the claims are confusing because method step (a) still recites "target tissue" (thus not limited to radiation resistant tumor) but any tissue may be a "target tissue" (e.g., see especially claims 2 and 3).

NCI teaches administration of SU6668 to a target tissue. SU6668 is a P13K inhibitor in treating patients with advance solid tumors (which contain epithelium and vasculature). Therefore the teaching of targeting a target tissue is met.

11. Claims 1-4, 6-7 and 15 stand rejected under 35 U.S.C. 102(b) as being anticipated by Laird et al. (2000), for the reasons made of record in Paper No. 20080606 and as follows.

Consistent with the 112-second paragraph rejection above (see paragraph 7) the claims are confusing because method step (a) still recites “target tissue” (thus not limited to radiation resistant tumor) but any tissue may be a “target tissue”.

Laird teaches vascular endothelial growth factor is associated with solid tissue and that SU6668 is a novel inhibitor of solid tumors. Increased radiosensitivity of the target tissue is produced by the administration of this PI3K antagonist, as recited in claim 1.

12. Claims 1-13 and 17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Durden (US 6,777,439) and Walker et al. (2000), in view of Weichselbaum et al (US 6,025365), for the reasons made of record in Paper No. 20080606 and as follows.

Applicant argues that the newly recited limitation as it applies to instant claim 1 and cancellation of claim 5 should render the rejection moot. Also Applicant argues that Weichselbaum et al. teaches the use of chelerythrine.

In response, this is found not persuasive because one of ordinary skill in the art would have been motivated to employ the teachings of Durden and Walker et al. to administer a P13k kinase inhibitor/antagonist (LY294002 or Wortmannin) to radiation resistant tumors such as brain tumors (as evidenced by Weichselbaum et al., see col. 11 lines 35). One of ordinary skill in the art would have been motivated to combine the cited prior art and administer a PI3K antagonist for increasing radiosensitivity in a targeted tissue because Durden teaches administering P13Kinase inhibitors. See col. 40, lines 54-60 of U.S. Patent 6777439.

Applicant's argument that Weichselbaum et al. teach the use of chelerythrine is found not persuasive because Weichselbaum et al. was only employed as an evidence to show that brain tumors are radiation resistant.

Finally, as to the administration of Wortmannin in the concentration claimed, one of ordinary skill in the art would have been motivated to optimize using the dosage having the optimum therapeutic index, which is well within the level of the ordinary skill in the art, in order to obtain the maximum effect of the drug.

13. Claims 1 and 15-16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Durden (US 6,777,439) in view of Ning et al. (2001) and National Cancer Institute (2001) further in view of Tang et al. (6,573,293) for the reasons made of record in paper no. 20080606 and as follows.

Applicant argues that Ning teaches SU6668 to enhance the efficacy of radiation therapy in mice bearing carcinoma and that Ning teaches the inhibition of tumor

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angiogenesis by administration of SU6668 which increases the hypoxic fraction of tumors and decreases the relative radiosensitivity of tumor cells. Applicant argues that Tang teaches pyrrole-substituted 2-indole compounds that modulate the activity of protein kinase disorders.

In response, the claim 1 is not limited to radiation resistant tumors but also to any target tissue, therefore Durden, Ning and Tang when combined makes the claimed invention obvious at the time the invention was made, for the reasons made of record.

In summary, Durden teach regulating p53 mediated gene expression by administering PI3kinase inhibitors to increase chemosensitivity/radiosensitivity of tumor cells (brain tumors), wherein the P13k antagonist is LY294002. See col. 2, lines 29-31, 45-55 and 64-67, col. 3, lines 1-3 and col. 7, lines 9-40; as required by instant claim 1.

Ning et al. teach SU6668 enhances the efficacy of radiation therapy in mice bearing carcinomas, as stated of record in the last office action, and NCI teaches administering SU6668 to patients (human-mammal) with solid tumors, in which administration at an optimal biological effective dose would have been obvious by using a minimal therapeutic index to minimize toxicity.

Tang et al. teach SU11248 is used to treat target tissues such as ovarian cancer, neck cancer (see col.175 and 46-67; as required by claim 16) in which one of ordinary skill in the art would have been motivated to administer LY294002, SU6668, SU11248 with a reasonable expectation of success of increasing radiosensitivity of a radiation resistant tumor.

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. V. G./  
Examiner, Art Unit 1618  
3/9/09

/Robert C. Hayes/  
Primary Examiner, Art Unit 1649